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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/059,447	01/29/2002	Daniel S. Smith	0994.00134	8310

7590 09/29/2004

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/059,447	SMITH, DANIEL S.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *5-8 and 10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are currently pending and are present for examination. Claims 1-4 and 9 are now under consideration. Claims 5-8, 10-12 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 7-19-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

It is noted that applicants have filed a set of colored drawings. Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. The following are particularly noted and requires applicant's attention.

a) Table 5 lists a full length sequence of an amino acid sequence. However, there is no SEQ ID NO allocated to that sequence nor a legend in the Table.

b)Applicants continue to list SEQ ID NO:15 in claim 9 while the total number of sequences in the application is only 12. Correction is required.

See particularly 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 is drawn to a recombinant α N-acetyl-D-galactosaminidase (NAG) as set in SEQ ID NO:1 and 8-15 and functional analogs thereof. However, according to the new sequence listing filed, the total number of sequences in the application are only 12. Therefore it

is not clear to the Examiner as to which specific SEQ ID NOs are encompassed by the claim. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 and claims 2-4 depending therefrom are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains new subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is drawn to polypeptides having 90% sequence homology to SEQ ID NO:1-10. A perusal of the specification indicates that applicants have no ample support for the current amendment claiming "90% homology". Therefore this is considered as new matter and the claim is rejected as possessing new matter. Applicants are urged to cancel the new matter introduced while responding to this Office action.

Claims 1-4 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single purified α-N-acetyl-D-galactosaminidase (NAG) purified from *C.perfringens* comprising the amino acid sequences SEQ ID NO:11, does not reasonably provide enablement for any homologs (functional or structural) having at least 90% homology to the peptide sequences set forth in SEQ ID NO:1-10 or functional analogs of the same (SEQ ID NO:1 and 8-12?). The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-4 and 9 are so broad as to encompass any NAG including variants, mutants and recombinants from any source having 90% amino acid identity to the short peptide fragments SEQ ID NO:1-10. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number NAG broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the single purified NAG. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the use of the full length SEQ ID NO: 11 as NAG but provides no guidance with regard to the making of variants and mutants or with regard to other uses. Furthermore as SEQ ID NO 1-10 comprise very short amino acid

sequences, those skilled in the art need to be provided highly specific guidance for making variants. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim. It should also be noted here that amino acid sequences that were found to be 90% homologous with for example SEQ ID NO:6 had entirely a different function that that of NAG (see enclosed sequence alignment at the end of this Office action).

While enzyme isolation, recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications to any NAG because the specification does not establish: (A) first of the full length amino acid sequence of the enzyme; (B) regions or specific amino acids of the protein structure which may be modified without affecting NAG activity; (B) the general tolerance of NAGs to

modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including homologs and functional analogs of *C.perfringens* NAG. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of NAGs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicant submits that the specification discloses what is defined as an analog and homolog and provides obtain homologs and analogs of the sequences recited in the claims. Further applicant argues that additional sequences as disclosed on pages 7 and 8 of the specification as filed provide homologs of the partial sequence and as such, provide guidance as to what is intended to be included as a "homolog." Examiner respectfully disagrees with such an argument as being persuasive to overcome the above rejection. Contrary to applicant's argument the sequences recited on pages 7 and 8 have been indicated as "internal sequences" and not homologous sequences. Therefore, recitation of internal sequences cannot be considered as ample guidance for making homologs. Applicant further argues that the claims have been amended to more specifically recite that the homologs must have at least 90%

homology to the sequences recited in the claims and that the techniques utilized to make modifications to the sequences, including insertions, substitutions, or deletions of a residue are well known to those of skill in the art and therefore, one of skill in the art can substitute residues based on the disclosure provided in the specification as originally filed. Here again Examiner begs to differ. This is because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants i.e., variants based on very short stretches of amino acids, requires that one of ordinary skill in the art know or be provided with guidance for the selection of specific amino acid residues that can be modified and which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of -NAGs to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

Claims 1-4 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of NAG, its homologs with a molecular weight of about 72 kD and functional analogs comprising specific 8-25 amino acid long peptide sequences. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification teaches the isolation and characterization of only a single species of NAG , i.e., that from *C.perfringens*. Moreover, the specification fails to describe any other representative species by sufficient identifying characteristics or properties to show that applicant was in possession of the claimed genus. The identifying characteristics recited in Claims 1, 4 and 9 , i.e., enzymatic activity, approximate molecular weight, and the 5 peptide sequences which together include just a partial structural description of the structure of the single disclosed species, do not include sufficient

characteristics to limit the claimed genus to proteins which are not highly variable in both structure and function. The claims include species in which a significant per cent of the amino acid sequence of the single disclosed species has been substituted. Therefore, the species within the genus are highly variable in structure. While Claim 3 adds two additional characteristic to the limitations of the genus of each of these claims, none of these characteristics, by itself is sufficient to change the fact that the claims include proteins which are highly variable in both structure. Thus for all the reasons discussed, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicant has traversed the above rejection arguing that the specification discloses what is defined as an analog and homolog and provides adequate descriptions of such homologs, such that one of skill in the art could easily obtain homologs and analogs of the sequences recited in the claims. Here also applicant argues that additional sequences as disclosed on pages 7 and 8 of the specification as filed provide homologs of the partial sequence and as such, provide guidance as to what is intended to be included as a "homolog". Examiner respectfully disagrees with such an argument. This is because the sequences disclosed on page 7 and 8 are not "additional" but the very same internal sequences. Further, even though the claims have been amended to more specifically recite that the homologs must have at least 90% homology to the sequences recited in the claims, they continue to lack written description because as stated earlier the characteristics claimed n claim 1

and 9 do not include sufficient characteristics to limit the claimed genus to proteins which are not highly variable in both structure and function.

Applicant also argues that the techniques utilized to make modifications to the sequences, including insertions, substitutions, or deletions of a residue are well known to those of skill in the art and therefore, one of skill in the art can substitute residues based on the disclosure provided in the specification as originally filed. While this argument is not pertinent to address the lack of description, Examiner maintains that even though the techniques may be well known, applicants have not provided enough guidance to make the variants as claimed. Hence the above rejection is maintained.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Levy et al. (J. Biol. Chem., 1980, Vol.

235(24):11737-11742). This rejection is based upon the public availability of a printed publication. Claims 1-4 and 9 of the instant application are drawn to a NAG enzyme isolated from *C.perfringens* having the characteristics listed in claims 2-4.

Levy et al. disclose the purification and properties of the NAG isolated from *C.perfringens*. The reference while disclosing that the isolated and purified enzyme has optimum pH in the neutral range (pH 6.5-7.0) and has a specific activity of more than 40.54 U/mg, does not specifically disclose the molecular size of the protein or the internal amino acid sequence of portions of the enzyme. However, as the enzyme in reference has been isolated from the same source as that claimed in the instant application, Examiner takes the position that the enzyme in the reference inherently has all the characteristics including the amino acid sequence as that claimed in the instant application. Therefore Levy et al. anticipate claims 1-4 and 9 as written. (Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art (specifically with respect to amino acid sequence), the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.)

In the alternative, with the reference of Levy et al. in hand, it would have been obvious to those skilled in the art to use alternate protein purification techniques and arrive at a more homogenous preparation of the NAG enzyme than that provided by the reference. One of ordinary skill in the art would have been motivated to do so as the enzyme has been shown to play an important role in blood biochemistry. One of ordinary skill in the art would have a

reasonable expectation of success since Levy et al. provide a reasonable pure enzyme preparation and the art provides more improvised protein purification methods. Therefore, the above invention would have been *prima facie* obvious to those skilled in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that the Levy et al. reference teaches a method of purification that results in a preparation contaminated with multiple species of enzyme and that it is postulated that the a-N-acetylgalactosaminidase is a multi-enzyme complex that needs to be dissociated. Applicant also argues that the final "dissociated" preparation measured 0.1%, 1.9%, and 1 .2% contamination with neuraminidase, B-galactosidase, and β -N- acetylglucosaminidase, respectively and therefore, the preparation in the reference cannot anticipate.
Applicant also argues that in the SDS-PAGE of the preparation, there is revealed multiple bands of a-N-acetylgalactosaminidase activity along with several other protein bands and that this is in contradistinction with the purified enzyme of the presently pending independent claims, wherein only one band is found on the SDS-Page of the final enzyme. Examiner respectfully disagrees with such an argument. This is because, claims are not limited to all the above but are only limited to "homogenous" preparation which can still consist of minor fractions of other proteins. Applicant also argues that the present invention has no detectable β -galactosidase or 6-N-acetylglucosaminidase activity and contains therein less than 0.8 ng of neuraminidase as detected per milligram of pure α -N-acetylgalactosaminidase and in comparison, the enzyme conglomeration of the Levy et al article contains approximately 62 ng of neuraminidase and accordingly, the enzyme of the presently pending independent claims has at least 77-fold greater neuraminidase removal than that of the Levy et al. article. Here again these arguments are not

persuasive to overcome the rejection as claims do not specifically encompass the above as limitations.

Next applicant argues on similar lines that the Levy et al. data is converted from micro moles of substrate dehydrolyzed per hour to micro moles hydrolyzed per minute and based on such data the Levy et al. preparations have a specific activity of 17.4 compared to the present mean activity of 42.4 for the enzyme of the presently pending independent claims. Examiner respectfully disagrees that such arguments are persuasive to overcome the rejection again because claims are not specifically drawn to such limitations. For all the above reasons, the rejection is maintained.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

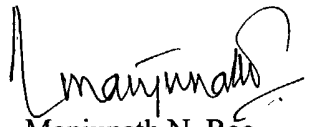
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 6.30 a.m. to 3.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0939. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.



Manjunath N. Rao
September 24, 2004